Cerebral cortex

↝ clear division between 2 halves along sagittal fissure

↝ Controls
- voluntary actions
- cognition
- perception / awareness

↝ mammals have more complex 6-layer structure of the cortex = neocortex

↝ Highly developed — no. of neurons related to "intelligence"

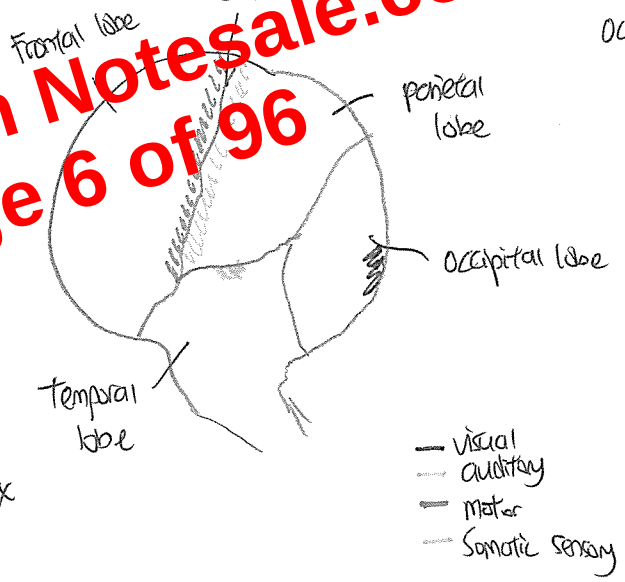
↝ Diff. sizes, same general structure

Cortical folding:

Problem - to ↑ intelligence need to ↑ processing power
- Cortical neurons represent processing power
- ↑ no. of cortical neurons

But, skull is confined structure, want to keep volume + mass to minimum
↳ big heads harder to protect than little ones

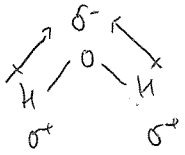
* Cortical lobes clockwise from the occipital, frontal, parietal, occipital, temporal

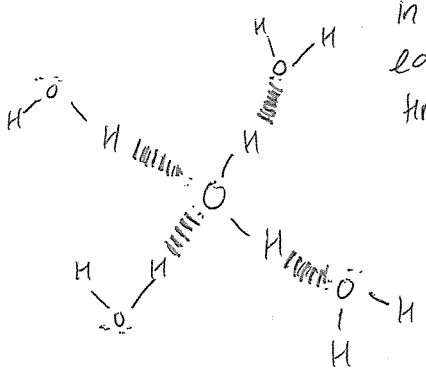


The Homunculus:
- A way of showing the location & amount of neocortex dedicated to a particular function
- proportional to neuronal composition NOT mass of body part
- Highlights the importance of controlling finger movements & speech in humans

Water ($M_r = 18$)

Statements: All life on Earth live in aqueous environment





In crystalline ice structure, each H_2O molecule forms H-B w/ 4 other H_2O molecules

liquid water – disorganized

solid (ice) – organized

Importance of ions

- carry signals in the body – action potentials
- act as an energy store – secondary active transport
- interact biochemically with proteins & other molecules
  - ↳ Ca^{2+} / troponin C in muscle contraction
  - ↳ Mg^{2+} / ATP

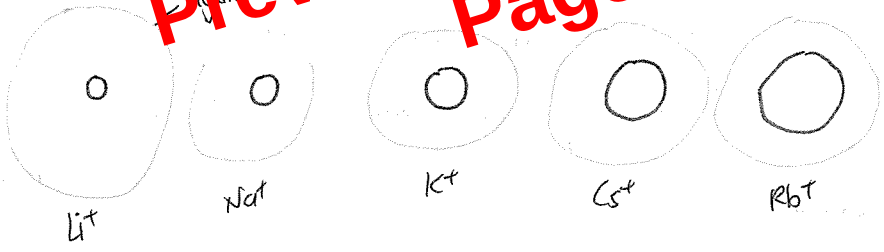
Basically important ions

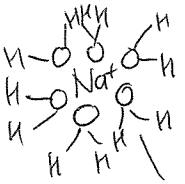
Ions which are physiologically useful
- Na^+
- K^+
- Cl^-

Ions which are biochemically useful
- Zn^{2+}, Mg^{2+}, Fe^{3+}
- trace metals

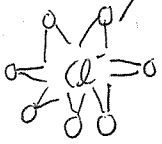
Ca^{2+} – both physiologically & biochemically useful

Excitable cells
- skeletal muscle
- cardiac muscle
- many hormone-secreting cell





primary hydration shell



- hydration shell affects mobility in solution
- hydration shell is the effective "size" of ion
- hydration shell affects interaction with proteins

Consequently, in biochemistry Li^+ would have a larger size than Rb^+

* ↝ smaller ion would attract more H_2O than a larger ion of the same charge as smaller ion would possess a greater charge density *

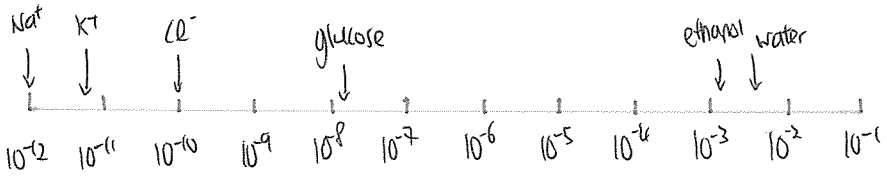
Membranes ⇝ All biological membranes are lipid bilayers

hydrophilic polar head
hydrophobic tail
} amphipathic nature drives formation of bilayers

* when phospholipid placed in water, entropy drives the formation of phospholipid bilayer

Membranes are essentially impermeable to ions:

⇝ glucose slightly more permeable than ions as it is less polar



Ion Gradients in cells:

Ion	Concentration outside (mM)	Concentration inside (mM)	Ratio
Na^+	150	15	10:1
K^+	5	100	1:20
Ca^{2+}	2	0.0002	10000:1
Cl^-	150	13	~11.5:1

* Ca^{2+} gradient always biggest

Making the gradient

(1) Want [ion] higher inside than outside, need to bring ions in into cell

(2) Want [ion] higher outside than inside, need to extrude ions

Membrane Proteins ⇝ allow cells to establish ion gradients and use them

⇝ must contain hydrophobic nature to be imbedded in lipid bilayer

Pumps

- Concentration of ion against gradient needs energy
- cells get this energy from hydrolysis of ATP
- cells used special proteins termed pumps
- pumps perform primary active transport

Basic Features of Pump
- live in membranes
- move ions 'uphill' [against conc gradient]
- Couple to ATP (usually)
- fairly slow
- nearly always move cation

eg: Na^+/K^+ ATPase
Ca^{2+} ATPase

The Sodium Pump: ~40%

⇝ Extremely important pump – cells expend 25% of ATP keeping it going (more in neurones)

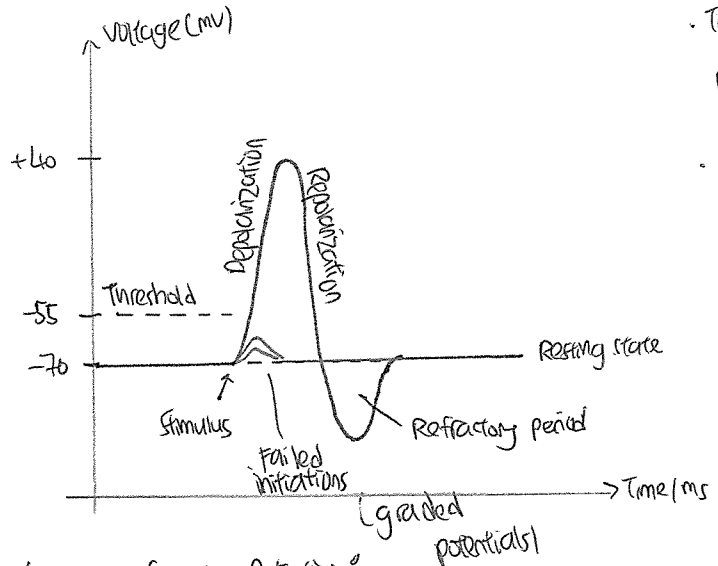
⇝ More correctly called Na^+/K^+ ATPase

⇝ Extrudes $3Na^+$ & $2K^+$ for every ATP hydrolysed

⇝ Generates a Na^+ & K^+ gradient
- Na^+ low in cytoplasm
- K^+ high in cytoplasm

⇝ causes the inside of cell to be negative when compared to the outside

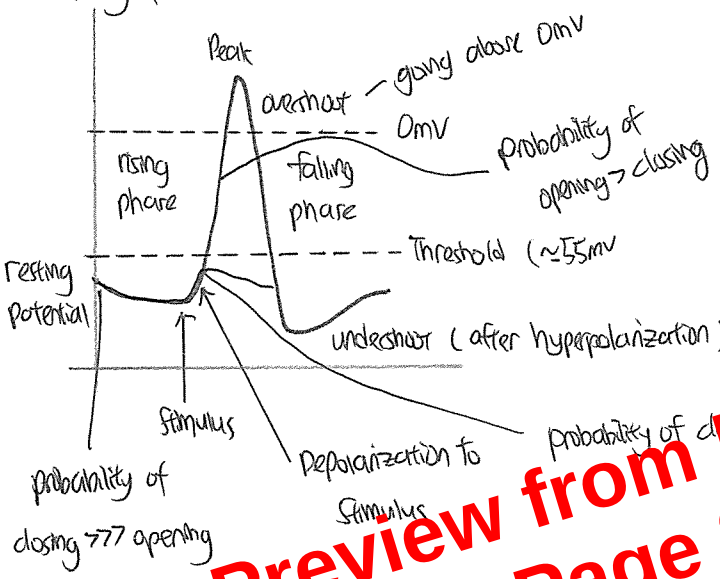
The Action Potential:



- Transient reversal of the membrane potential [from the inside-negative resting potential to inside-positive]
- Duration can vary from a few ms (nerve, skeletal muscle) to a few hundred ms (heart)
- Action potentials are all or none ← below threshold-no action potential
- larger stimulus – fixed size of action potential
- body codes stimulus intensity by frequency NOT size of action potential

[graded potentials]

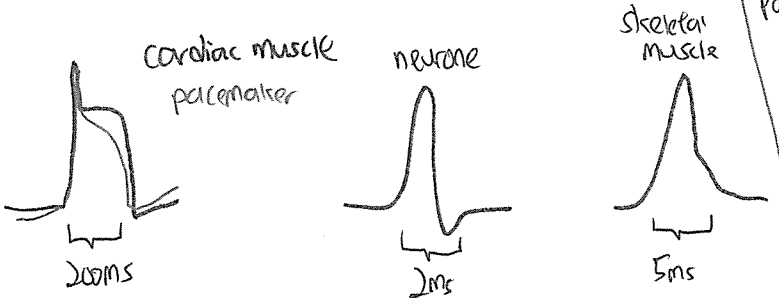
Anatomy of Action Potential:



- graded potential – membrane potential's small change due to a sub-threshold stimulus
- depolarization changes the probability of the channels to open
  - opening sodium channels → depolarization
  - [* one direction transmission of AP → orthodromic conduction
  - opposite direction → antidromic conduction]

Voltage clamp → allow the membrane potential of axon to be clamped at any value desired.

Patch clamp → Sealing tip of electrode to a very small patch of neuronal membrane
→ only 1 channel contained in the patch
→ membrane potential can be "clamped" at any value



↓ way ↑ duration than action potential in neurones & skeletal muscles

Same sort of ion channels, hence operate more or less the same way

* Single amino acid mutation of gene coding for Nav channels can result in [generalized epilepsy w febrile seizures.] → channelopathy, human genetic disease caused by alterations in structure & function of ion channels.

↓

fever

The Axonal Solution – to get fast transmission, we want axons w big length constants

– length constant depends on R_m, R_i and diameter

R_m – leakiness; R_i – conductivity (resistance)

Nature's option:

↑ R_m, better insulation

↓ R_i, better conducting cores (X)

↑ diameter, fatter cables (non viable in complex organism, only viable in simpler organisms)

R_m – resistance of membrane

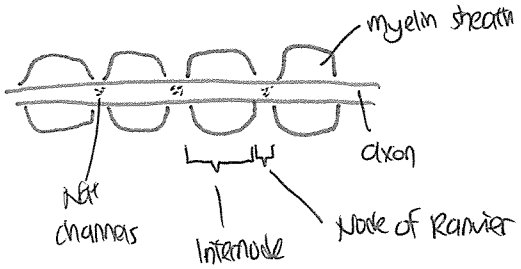
A) increase axonal diameter: strategy used by primitive animals eg: squid – rapid escape from danger

Problem: not good for animals w complex nervous system – FAT heads

B) decrease leak of current: myelinating axons

→ jumping conduction

- Effectively: current jumps btwn ahead "saltatory" conduction
- internodes about 1mm long and spaced at regular intervals
- Repolarization only occurs at the nodes
- myelination is specific to axons however NOT all axons myelinated
- myelination ↓ capacitance of axons ~~by~~ giving bigger charge separation



Cross section of myelinated Neurone:

→ diffusion of Nat is fast but AP is relatively ~~so~~ slow

↝ Schwann cell / oligodendrocyte provide nutrients to ~~axon~~ axons

Sequences in myelination formation: rotary sheath migration

can be upto 100+ layers thick

Node of Ranvier:

- High density of Nat channel (10,000 /μm^2)
- In axon under myelin ie: internodal region Nat channel density very low (100/μm^2)
- In unmyelinated axons, Nat channel density moderate (1000 /μm^2)
- Higher density of channels in node decrease rise time of AP, firing of action potential is easier } faster

Sensory fibre nerve fibre types:

Axon Type	Myelinated	Diameter (μm)	Conduction Velocity (m/s)
Aα	✓	12-20	80-120
Aβ	✓	10-12	30-70
Aδ	✓	1-5	5-30
C	X	0.2-1.5	0.5-2.0

* Vitamin D may help reduce prevalence of multiple-sclerosis. Epidemiology suggests the further you live away from the equator, the more likely you are to have MS *

Advantages of Myelination
- speed
- compactness of neurones
- energy efficiency — move ions at a smaller section of axons, ↓ATP used as ↓ Na^+/K^+ ATPase used

Diseases Involving Altered Myelination

1) Multiple Sclerosis
- immune mediated (autoimmune disease)
- demyelinating disease
- central nervous system
- can be treated be corticosteroids

↝ myelin sheath revealed by staining w fluorescent antibodies to myelin basic protein

↝ bare axon revealed by staining w fluorescent antibodies to the cytoskeletal protein neurofilament *

* In unmyelinated neurones, transmission slow but still occurs *

↝ damage to myelin sheath

↝ decreased conduction in axons

↝ NOT simply as reverting to non-myelinated axons as Na+ channels remain concentrated where Nodes of Ranvier are

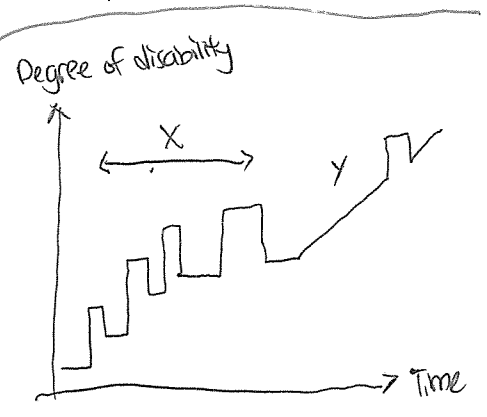
Symptoms experienced in multiple sclerosis

Deficit Reported	Prevalence	During Whole Disease
Visual / Oculomotor	69%	100%
Paresis	43%	88%
Paraesthesia	41%	87%
Incoordination	23%	82%
Genitourinary / Bowel	10%	63%
Cerebral	4%	39%

↝ enhancing lesions / cerebral atrophy in multiple sclerosis

↝ optic nerve very vulnerable to immune system attack

↝ almost all multiple sclerosis patients have visual impairments



primary-progressive / progressive-relapsing

X - relapsing emitting phase

Y - secondary-progressive phase

Guillain-Barré syndrome: autoimmune attack on myelin in PNS

Simple test for multiple sclerosis ↝ visual evoked potential

In all autoimmune disease, women are 2-3 times more likely to be affected when compared to men

Spontaneous neurotransmitter release persists in the absence of APs and/or Ca^{2+} leading to miniature PSP
[The vesicle hypothesis]

Miniature postsynaptic potentials ("minis")
↳ response ∝ no. of vesicles release

- occur spontaneously, even in zero extracellular Ca^{2+}
- have amplitudes that are multiples of a quantal unit
- due to release of one / a few quanta (vesicles)

(1) quantum = release of transmitter from a single vesicle

- As extracellular Ca^{2+} is lowered, PSP amplitude ↓ in a step-wise manner (due to ↓ in no. of quanta)
- Quantal analysis of AP-evoked PSPs show that they involve release of up to 200 quanta per AP.

Quantal content = no. of quanta released per AP

- Each quantum contains several thousands of Ach

Release of Neurotransmitter by exocytosis

1) Docking (Ca_i-dependent)
2) Ca^{2+} influx
3) Membrane fusion
4) Vesicle recycling

Elevated Ca^{2+} in presynaptic terminal triggers release of neurotransmitter from 'docked' synaptic vesicle

e-SNARE, v-SNARE } anchor vesicle to membrane during docking

{ v-SNARE in vesicle membrane
t-SNARE in presynaptic membrane }

- Voltage-gated calcium channel
- Synaptotagmin – triggers change in conformation of SNARE proteins
- vesicle fuses w terminal membrane, vesicle membrane is recycled to form new vesicles
- Botulinum toxin disrupts formation of SNARE complex

Heteroreceptor: respond to a diff. neurotransmitter unlike auto receptors [also found on presynaptic membrane]

Specific example → In striatum, there is ↑ dopaminergic synapses. ↑ release of dopamine caused by nAchR on presynaptic membrane

when nAchR activated, presynaptic membrane becomes more depolarized leading to ↑ Ca^{2+} influx

lack of dopamine → Parkinson's

excess dopamine → involved in some symptoms of schizophrenia

Hyperekplexia : Startle disease

↳ means excessive startle. An affected adult will startle easily at a sudden sound / unexpected touch and may fall and be injured. Fall will be stiff & fast. Usually inherited as an autosomal dominant trait.

↳ single amino acid mutation in the glycine receptor (Cl^- ion channel) → can lead to seizures of epilepsy

CNS inhibition ↓ as Cl^- open less frequently

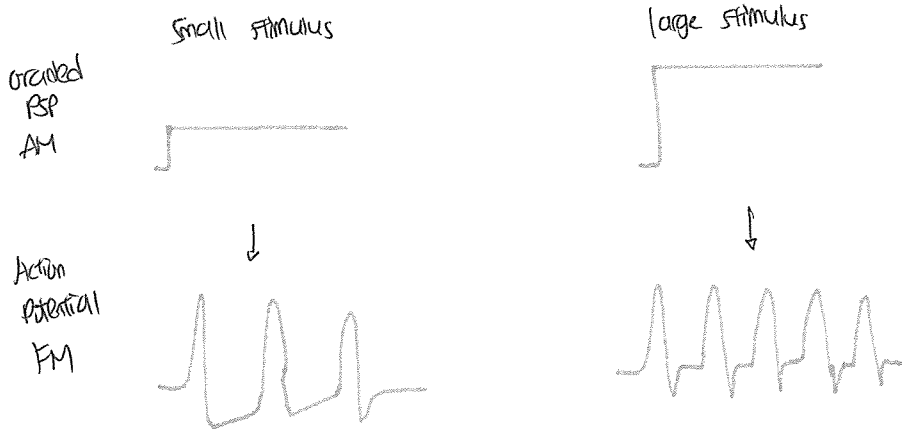
↳ important inhibition receptors

mouse – spasmodic

cattle – spastic

Encoding - converting AM to FM at the axon hillock

* Neurons use an FM code as both frequency & pattern of AP conveys information



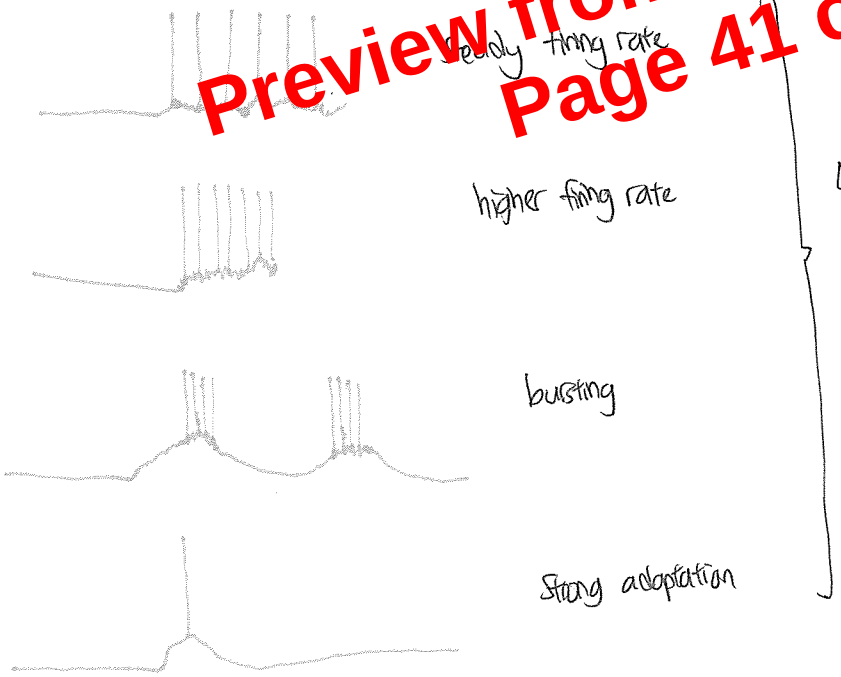
AM - amplitude modulated

FM - frequency modulated

↑ amplitude, ↑ frequency

Diversity of neuronal responses to the same input:

- The nature of information conveyed by the post synaptic neuron depends on synaptic input & neuron's response properties



4 diff. neurons MAY be able to generate four diff. response ↓ depends on the diff. ion channels present on the neurons.

Proprioception from Muscle Spindles:

- deep within most skeletal muscles are specialized structures → muscle spindles
- muscle spindle aka stretch receptors contain several types of specialized skeletal muscle fibres in a fibrous capsule. In the middle (equatorial) region, group Ia sensory axons wrap around muscle fibres of the spindle
- spindles and their associated axons detect changes in muscle length ~> proprioceptors
- group Ia neurons synapse w/ alpha motor neurons in the spinal cord

~~Myotatic Reflex~~
Myotatic Reflex:

- also known as stretch reflex
- moves sensory feedback from the muscle
- rate of discharge of Ia sensory axons is closely related to length of muscles
- as muscle is stretched, discharge rate ↑ ; as muscle shortens, discharge rate ↓
- Ia axon } alpha motor neurons constitutes the monosynaptic myotatic reflex because only one synapse separates the primary sensory input from the motor neuron [no interneurons in spinal cord for this pathway]
- serve as antigravity feedback loop: when a weight is placed on the muscle, causing it to stretched, the Ia axon [illegible] depolarise due to opening of mechanosensitive ion channels. This increased amount of AP from Ia axons synoptically depolarizes the alpha motor neurons, causing muscle to contract.
- Eg: knee-jerk reflex, stretch reflex (described above)

Cardiac Muscle → Broadly similar to skeletal muscle

↳ cells incompletely fused → forming gap junctions + desmosomes = electrically connected
↳ anchor mechanically

↳ joined by intercalated discs into a branched syncytium
↓
acts as a single unit

↳ control mechanisms different [heart's contraction doesn't require neuronal action]

↳ Diff. subtypes of myosin, actin

↳ Action potentials different

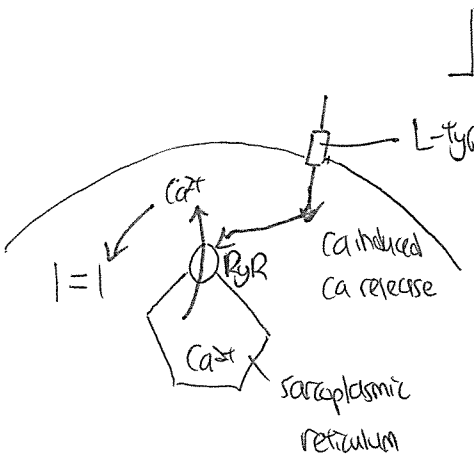
↳ Excitation-contraction coupling different

↳ only found in ♡
↳ myogenic contraction

Cardiac Excitation Contraction Coupling

→ no physical linkage between RyR and L-type Ca- channel

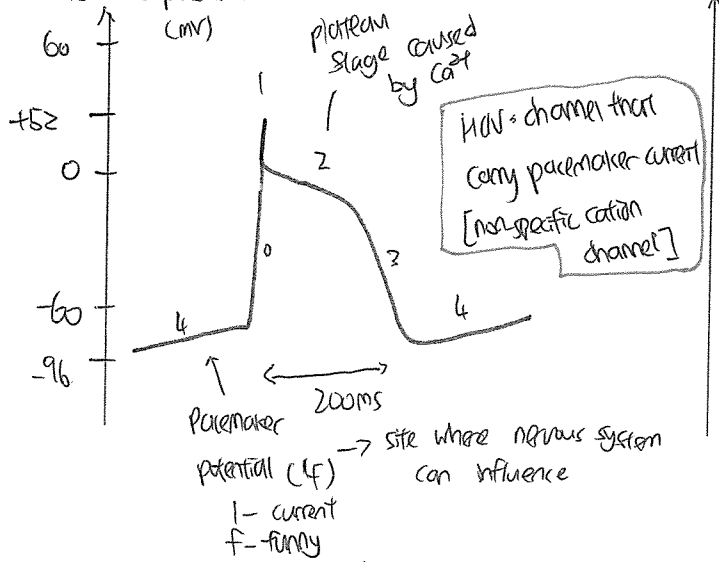
→ RyR stimulated by Ca^{2+} entry via L-type Ca^{2+} channels



Sources of Ca

- 15% - 20% Ca current from outside
- 80 - 90% from SR via CICR

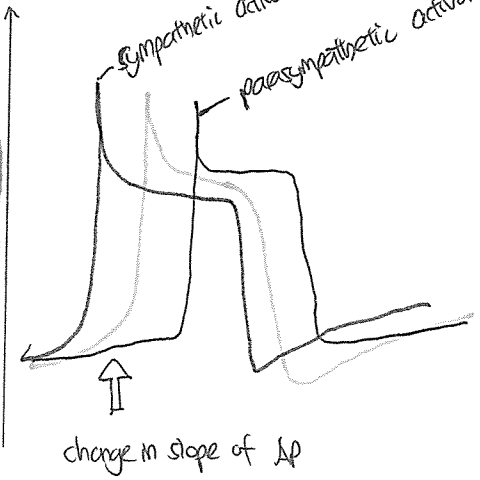
Initiation of Contraction of Cardiac AP



→ site where nervous system can influence

I- current
f- funny

Coupling Contraction



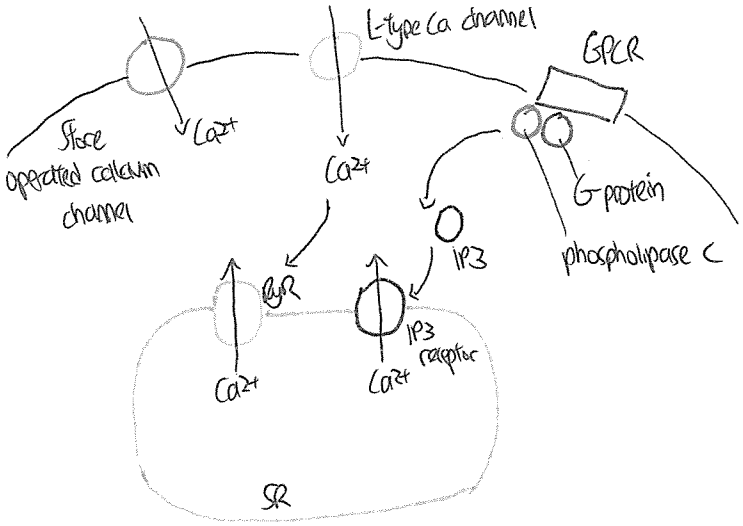
→ Force of contraction determined by

- degree of stretch of cardiac muscle [Starling's Law of Heart]
- conc. of cytoplasmic Ca^{2+} - this can be modulated by the ANS

SNS - increase
PNS - decrease

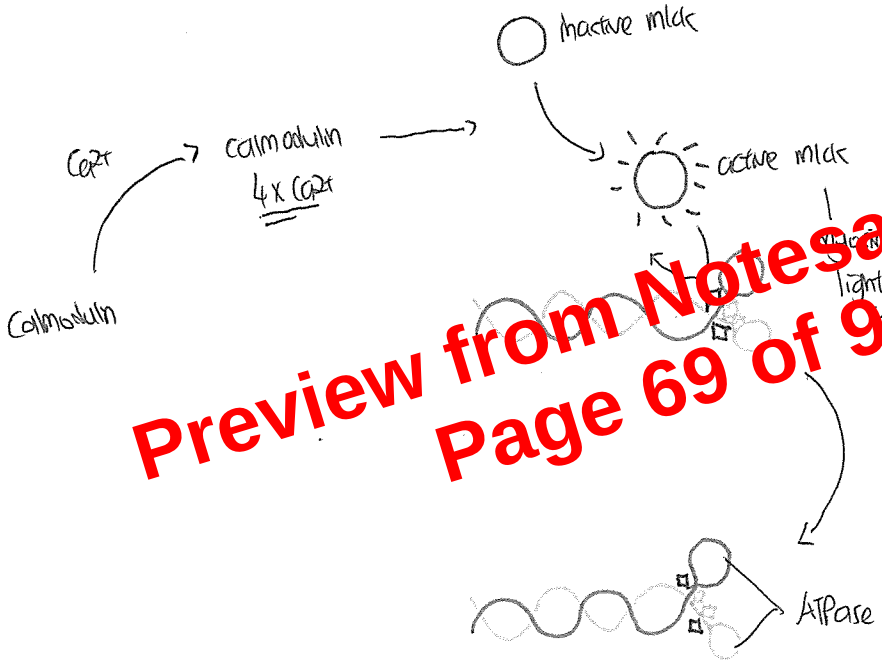
→ Much of the current in cardiac muscle is carried by L-type voltage sensitive Ca channels which inactivates more slowly hence causing a plateau phase

Sources of Calcium



- When SR becomes exhausted of Ca^{2+}, store operated Ca channels allows further influx of Ca^{2+} into the cell

phospholipase C hydrolyses PIP2 phosphatidyl 4,5-bisphosphate into IP3 + DAG



- myosin head has ↑ ATPase activity unless regulatory light chain is phosphorylated by mlck

To switch off this signal, Ca^{2+} has to removed. Next, myosin light chain phosphatase removes P_i from regulatory light chains -

These involvement of enzymes means that smooth muscle contraction and relaxation is a slow process

Smooth Muscle Excitation

- can be myogenic — some smooth muscles eg: gut have pacemaker-like activity
- can be initiated by AP triggered by neuronal stimulation
- can get AP superimposed on myogenic activity
- can be a graded response to depolarisation (no AP)
- can be modulated by neurotransmitters / hormones

Pathophysiology of Sarin : An irreversible cholinesterase inhibitor

n) nAchR has a desensitized state which is a kind of safety mechanism that receptor switches on after it is exposed to Ach for a long time.

n) When nAchRs are open continuously, muscle will be continuously depolarized thus will not be able to fire further action potentials because the voltage-gated Nat channels will be largely inactivated.

n) If Ach persist too long in a cholinergic synapse, AchR will be desensitized

Molecular Mechanism of Sarin

- enzymatic mechanism centres around a group of 3 amino acids : serine, glutamate and histidine.
- serine receives acetate group from Ach to release free choline
- Acetyl- serine residue is then broken down to recycle the active site
- sarin attaches to the serine residue

Antidotes to Sarin – atropine : antagonist at muscarinic Ach receptors

pralidoxime : recycles cholinesterase back to its active form, only effective if administered very quickly after exposure

Brain killers

- Stroke
- brain injury ← caused by sporting injury
- multiple sclerosis
- Parkinson's disease
- Motor neuron's disease
- Alzheimer disease
- Brain tumour
- Epilepsy
- CJD (prion, Mad Cow disease)
  - neuronal damage / death
  - acute vs. chronic
  - causes, treatments
  - understandings / research

Stroke

↳ reduced blood flow and oxygen to brain, also lead up to build up of CO_2
↳ many organs can survive with ↓ $[O_2]$ but NOT brain
↳ 3rd greatest killer
↳ causes - brain artery blocks
- brain artery bleeds < intracranial haemorrhage, subarachnoid haemorrhage
- poor general circulation
- heart failure
- drowning → asphyxiation
- too low O_2 at birth

Brain accounts for
- 2-3% of body weight
- 15% of cardiac output
- 20% of all O_2
- 25% of all glucose, brain does NOT metabolize fatty acids
- critically dependent on a constant blood supply

↳ limited treatment: during surgery, brain cooled down to (4) 31-32°C to reduce brain activity, hence reduce risks

An efficient "transport system" for the brain
In: O_2, carbohydrates, amino acids, hormones, vitamins
out: CO_2, NH_3, lactate, hormones
* brain is very sensitive to pH changes

CO_2, NH_3, lactate } lead to acidic environment which is non-desirable for brain

Stroke risk factors:
- atherosclerosis
- age
- diabetes (doubles the risk)
- ethnic origin (more common in African Caribbean people)
- excessive alcohol
- family history of stroke (genetic predisposition)
- heart disease
- high BP, cholesterol
- obesity } inactive lifestyle
- smoking

Stroke symptoms → can be painless, silent

1) sudden severe headache with no known cause
2) unexplained dizziness, unsteadiness / sudden falls
3) sudden difficulty of speaking / trouble understanding speech
4) sudden dimness / loss of vision, particularly in one eye (stroke is usually unilateral → only affects (1) side of the brain)
5) sudden weakness / numbness of the face, arm or leg on one side of the body

Facial weakness
Arm & leg weakness
Speech problems
Test these signs

F.A.S.T.

Stroke – reduced blood flow ↓ O_2 to the brain

- 2nd greatest killer
- causes: brain artery block, brain artery bleeds, poor general circulation
  heart failure, drowning, low O_2 at birth
- limited treatment

Reason for failures of clinical trials
↳ time of treatment
↳ not successful when replicated
↳ treatment: there is many diff. types of stroke
↳ wrong target eg: NMDA receptors are important for normal physiology

general assumption that there is only (1) type of stroke

Preclinical & Clinical Stroke Studies
- over 1000 agents have been tested in experimental stroke models
- over 100 have made it to clinical trial
- still no widely effective pharmaceutical treatment for stroke in clinic

Recent failures
↳ NXY059 (anti-oxidant spin trap inhibitor)
↳ Gavestinel (glycine co-receptor antagonist)
↳ Cerestat (non-competitive NMDA blocker)
↳ Selfotel (competitive NMDA blocker)
↳ Clomethiazole (anti-epileptic; GABA agonist)
↳ Citicoline (membrane stabilisation, reduces free radicals)
↳ Lubeluzole (Nat channel blocker)
↳ Anti-ICAM1 (anti-adhesion molecule)

"high risk disease area"
expensive clinical evaluation

Inflammation
- response of immune system to infection or tissue damage
- 1st defined by Cornelius Celsus (AD 30)
- characterised by the following – heat (calor)
  redness (rubor)
  swelling (tumor)
  pain (dolor)
  loss of function (functiolaesa)

Inflammation and disease
condition
- arthritis
- asthma
- atherosclerosis
- cancer
- CNS disease
- diabetes
- IBS
- obesity
- Psoriasis

Inflammatory Mediators
- Glial cell activation (astrocytes, microglia) * IMPORTANT!!
- oedema indicating ↑ pressure
- systemic acute phase response
- expression of adhesion molecules
- invasion of immune cells
- synthesis of inflammatory mediators eg: cytokines, free radicals, prostaglandins

} events occuring following on inflammation

Poor translation from bench to bedside ...

Lack of studies considering relevant risk factors for stroke

Risk Factors for Stroke

Not modifiable
- Age
- Gender
- Heredity
- Race
- Geographic location
- climate

Modifiable well established
- high BP
- heart disease
- diabetes mellitus
- TIA
- atherosclerosis

Modifiable not well established
- high blood cholesterol
- low physical activity
- smoking
- alcohol abuse
- obesity
- infections

↗ clear mismatch between experimental & clinical situation

Co-morbid Animals
- homozygous cp/cp (corpulent) rat
  - ↳ obese
  - ↳ insulin resistant
  - ↳ atherosclerotic
  - ↳ Aged
- heterozygous +/cp - lean
- Atherogenic mouse - Apo E$^{-/-}$ mice + high fat / cholate diet
- S. pneumoniae infection pre-stroke

→ Microglia activation in corpulent rats

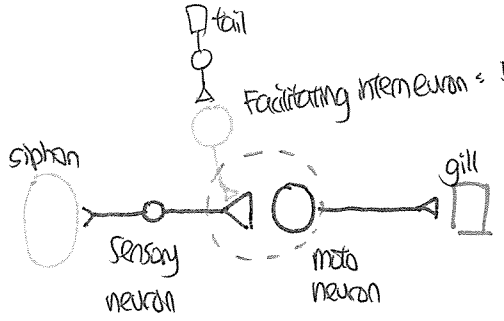
→ IL-1Ra effective with co-morbidity

→ infection increases ↓ stroke damage

→ Delayed IL-1Ra in aged lean rats

→ IL-1Ra still protects ↓ tPA

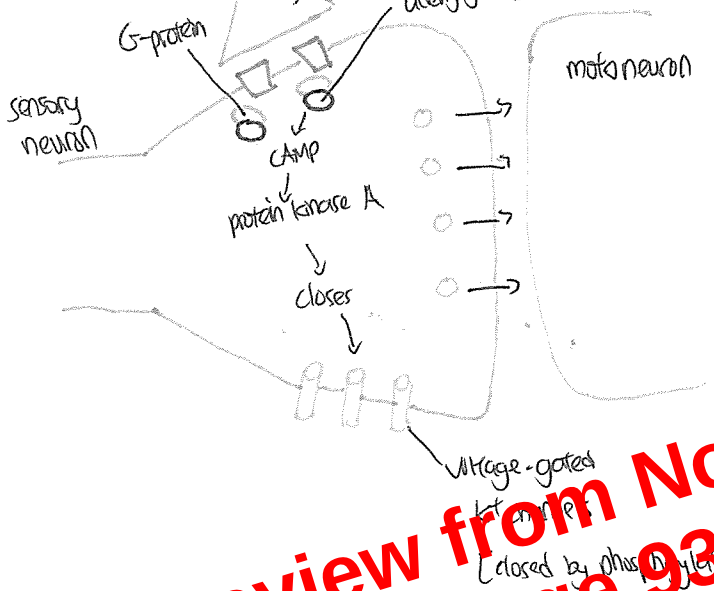
Sensitisation of gill withdrawal involves presynaptic facilitation – a form of synaptic plasticity



Facilitating interneuron = 5HT, synapses onto the presynaptic membrane of sensory neurone

How it all works – short term

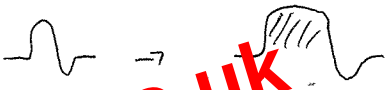
facilitating interneuron = 5HT, 5-hydroxytryptamine (Serotonin)



delayed repolarisation

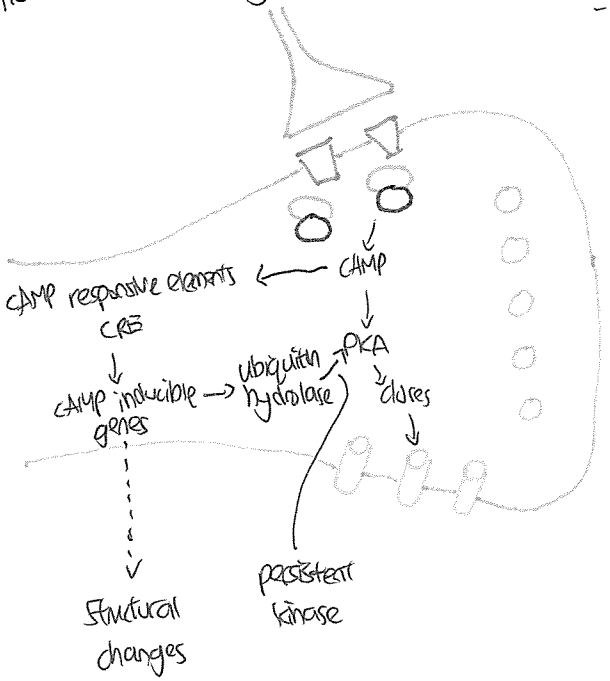
↑

- when K^+ channels are inhibited, less K^+ efflux, increased neurotransmitter release due to greater Ca^{2+} influx



greater area under graph which is proportional to amount of neurotransmitter release

How it all works – long term



- multiple shocks lead to ↑ cAMP
- ubiquitin hydrolase, an enzyme that persistently produce protein kinase A
- increased branching of neurones (structural changes)